4. (Once Amended) The polypeptide of claim 1, comprising at least the amino acid sequence from residue 4 through 172 of SEQ ID NO:4.

5. (Once Amended) An isolated polynucleotide encoding the polypeptide of claim 1 or a complement thereof.

15. (New) An isolated polypeptide selected from the group consisting of

(a) an amino acid sequence comprising SEQ ID NO:4;

(b) an amino acid sequence comprising residue 4 through 74 of SEQ ID NO:4;

(c) an amino acid sequence consisting of residue 75 through 172 of SEQ ID NO:4;

(d) a fragment of (b) or (c);

(e) an amino acid sequence comprising residue 4 through 74 of SEQ ID NO:4 and a portion of residue 75 through 172 of SEQ ID NO:4; and

(f) an amino acid sequence comprising residue 4 through 172 of SEQ ID NO:4;

wherein the polypeptide has mitogenic activity and does not consist of SEQ ID NO:2.

16. (New) An expression vector comprising the polynucleotide of claim 5.

17. (New) A host cell comprising the polynucleotide of claim 5.

18. (New) A method of producing a polypeptide, the method comprising:

(a) culturing the polynucleotide of claim 5 under conditions suitable for formation of the polypeptide; and

(b) recovering the polypeptide.

REMARKS

Justification for the amendments is as follows. Support for the isolated fragment of CTGF in claim 1 can be found in the specification, e.g., on page 7, line 12. Support for the expression vector in claim 16 can be found in the specification, e.g., on page 14, line 26, to page 15, line 2. Support for host cells in claim 17 can be found in the specification, e.g., on page 15, line 12, to page 16, line 2. Support for the method of producing a polypeptide in claim 18 can be found in the specification, e.g., on page 14, line 26, to page 21, line 21.

No new matter has been added by any of the amendments and entry of the amendments is respectfully requested. Attached hereto is a marked-up version of the changes made by the present amendment. The attached page is captioned "Version with markings to show changes made."

Formal Matters

The Examiner required amendment of the claims to comply with 37 C.F.R. §1.821(2)(d). Specifically, the Examiner noted that claims 2 and 3 reference regions of the sequence set forth in Figure 2, and stated that the claims should reference the Sequence Listing. Accordingly, Applicants have amended claims 2 and 3 to reference SEQ ID NO:4 rather than Figure 2.

Rejections under 35 U.S.C. §101

The Examiner rejected claims 1-5 under 35 U.S.C. §101. Specifically, the Examiner stated "[t]he claims read on products of nature, as fragments of CTGF are known to occur in nature, as are polynucleotides encoding such." (Office Action, page 3, lines 26-27.) The Examiner further stated "[a]mendment of the claims to indicate that the claimed products are isolated, purified, or to otherwise show the hand of the inventor would be remedial." (Office Action, page 3, line 27-28.)

Applicants have amended claim 1 to recite "isolated polypeptide" and claim 5 to recite "isolated polynucleotide", as suggested by the Examiner. The rejection of claims 1-5 under 35 U.S.C. §101 is thus moot, and withdrawal of the rejection of these claims under this section is respectfully requested.

Rejections Under 35 U.S.C. §112, 2nd paragraph

The Examiner rejected claim 5 under 35 U.S.C. §112, 2nd paragraph. The Examiner stated "[i]t is not clear whether the claim is encoded [sic] to a polynucleotide which encodes only the fragment of claim 1, or whether a full-length polynucleotide is encompassed, as such would comprise a region encoding said fragment." (Office Action, page 4, lines 8-10.)

As amended, claim 5 depends from claim 15, and the term "fragment" does not appear in claim 5. The rejection of claim 5 under 35 U.S.C. §112, 2nd paragraph, is thus moot, and withdrawal of the rejection is respectfully requested.

Rejections Under 35 U.S.C. §102

The Examiner rejected claims 1, 3, and 5 under 35 U.S.C. §102(b) as being anticipated by Brigstock et al., U.S. Patent No. 5,876,730. Specifically, the Examiner stated

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> Brigstock et al. disclose and claim HBGF and nucleic acids encoding such; ... It is noted that a polypeptide beginning at amino acid residue 248 from the N-terminus of CTGF, as claimed in claim 3 of Brigstock et al., would comprise exon 5 as set forth in Figure 2 of the instant application, which corresponds to residue 252. HBGF is disclosed as being mitogenic, ... (Office Action, page 4, lines 23-27.)

This rejection is respectfully traversed.

As amended, claim 1 recites "[a]n isolated polypeptide having mitogenic activity, and comprising the amino acid sequence of SEQ ID NO:4, ..." and claim 3 recites "[t]he polypeptide of claim 1, consisting of the amino acid sequence from residue 75 through 172 of SEQ ID NO:4"... As Brigstock et al. does not disclose the specific sequences recited in amended claims 1 and 3, these claims are not anticipated by Brigstock et al. Therefore, Applicants respectfully request withdrawal of the rejection of claims 1, 3, and 5 under 35 U.S.C. §102(b) as being anticipated by Brigstock et al.

The Examiner rejected claims 1 and 5 under 35 U.S.C. §102(b) as being anticipated by Grotendorst et al., U.S. Patent No. 5,408,040. The Examiner stated "Grotendorst discloses CTGF and nucleic acids encoding such. At column 3 lines 15-17 and 26-29, Grotendorst clearly indicates that functional fragments of the protein and nucleic acids ... are envisioned." (Office Action, page 5, lines 3-5.)

Grotendorst et al. states "CTGF polypeptide includes functional fragments of the polypeptide, so long as the mitogenic and chemotactic activities of CTGF are retained." (column 3, lines 15-17). Grotendorst et al. does not define the specific CTGF fragments identified in the present invention or the activities specifically associated with these fragments. In contrast, Applicants' specification demonstrates that fragments of CTGF can produce different and distinct activities. (See the present specification at, e.g., page 4, lines1 through 3.) Once such knowledge is obtained, one of skill in the art can, e.g., more precisely direct therapies associated with one activity of a molecule without affecting other, potentially undesirable activities. (See, e.g., Heffernan et al. (2000) Am J Physiol Endocrinol Metab 279:E501-E507, wherein N- and C-terminal fragments of human growth hormone show distinct and separable activities toward hypoglycemic and lipid mobilizing functions, respectively, of the intact molecule.) In summary, the present invention is directed toward a unique group of CTGF fragments not delineated by Grotendorst et al. Therefore, the specific CTGF fragments of the invention are not anticipated by Grotendorst et al., and Applicants respectfully request withdrawal of the rejection of claims 1 and 5 under 35 U.S.C. §102(b).

Rejections Under 35 U.S.C. §103

The Examiner rejected claims 2-4 under 35 U.S.C. §103(a) as being unpatentable over Grotendorst et al.,

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U.S. Patent No. 5,408,040, in view of Brigstock et al., U.S. Patent No. 5,876,730. Specifically, the Examiner stated

> Grotendorst et al. do not specifically suggest fragments comprising exons 4 and/or 5. However, it is noted that exons 4 and 5 consist of the carboxyl terminal 169 amino acids, or 48% of the CTGF polypeptide. It is common in the art to make such deletions by successively deleting portions from the ends of the molecule, often if not usually starting at the amino terminus of the protein. As Grotendorst et al. specifically suggest making functional fragments of CTGF, the Examiner finds that, using only the teachings of Grotendorst and routine experimentation (deleting portions of the protein and testing for activity), one of ordinary skill in the art would arrive at numerous species within the metes and bounds of the rejected claims. Further, given Brigstock's disclosure that HBGF, which is residues 247-349 of CTGF has mitogenic activity, one would expect success at making such fragments, and additionally would expect that fragments comprising at least residues 247-349, which comprise the entirety of the portion of the protein encoded by exon 5, would be active. (Office Action, page 5, line 25, to page 6, line 4.)

For a rejection under 35 U.S.C. §103(a) to be proper, all elements of the claim must be taught or suggested by the prior art reference(s). (MPEP §706.02(j), 8th Edition, pp. 700-31.) Neither Brigstock et al. nor Grotendorst et al. teach the specific CTGF fragments of the present invention. It is known in the art that, in many cases, the function of a fragment of a protein is unexpected and surprising in light of the function of the whole protein. For example, although an entire receptor may actively stimulate cellular activity when bound by an extracellular ligand, a fragment comprising the extracellular domain may act as an inhibitor of signaling. (See, e.g., Gray et al. (1990) Proc. Natl. Acad. Sci. USA 87:7380-7384; and Kohno et al. (1990) Proc. Natl. Acad. Sci. 87:8331-8335.) Such activities are not always obvious based on the sequence and activity of the protein as a whole. As stated above, fragments of CTGF can produce different and contrasting activities and only a subset of CTGF fragments stimulate mitogenic activity. As the present invention is directed toward a unique group of CTGF fragments not delineated by Brigstock et al. or Grotendorst et al., claims 2-4 are patentable over Grotendorst et al. and Brigstock et al., taken each singly or both in combination. Therefore, Applicants respectfully request withdrawal of the rejection of claims 2-4 under 35 U.S.C. §103(a).

Double Patenting Rejections

The Examiner provisionally rejected claims 1-5 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of copending U.S. Application Serial No. 09/461,688. The Examiner stated "[a]lthough the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to fragments of CTGF and nucleic acids encoding such. Although the two applications require different biological activities of those

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fragments, and are thus of different scope, there is substantial overlap in the actual fragments that are encompassed by the two sets of claims." (Office Action, page 6, lines 23-27.)

With respect to the Examiner's rejection under the judicially created doctrine of obviousness type double patenting, in the event the Examiner requires the filing of a terminal disclaimer to expedite prosecution of the present application, Applicants will consider filing such terminal disclaimer upon allowance of the relevant claims.

CONCLUSION

In view of the foregoing, Applicants submit that the claims are fully in condition for allowance and request early notification to that effect. If the Examiner has any questions regarding the present communication or the above-referenced application, please call Applicants' Agent at 650-866-7265.

Applicants believe that no fee is due with this communication. If, however, the Commissioner determines that a fee is due, the Commissioner is hereby authorized to charge any necessary fees to Deposit Account No. **50-0811**. **This form is enclosed in duplicate.**

Respectfully submitted,

DATE: 23 Apr 02

Christopher Turner, Ph.D.
Reg. No. 45,167 for Reg No 42,090

FibroGen, Inc.
225 Gateway Boulevard
South San Francisco CA 94080
Main: 650-866-7200
Direct: 650-866-7265
Facsimile: 650-866-7292

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

Claims 1-5 have been amended and new claims 15-18 have been added as follows.

1. (Once Amended) An isolated [fragment of connective tissue growth factor (CTGF)] polypeptide having mitogenic activity, and comprising the amino acid sequence of SEQ ID NO:4, wherein the polypeptide does not consist of the sequence of SEQ ID NO:2.

2. (Once Amended) The polypeptide [fragment] of claim 1, comprising at least the [an] amino acid sequence from residue 4 through residue 74 of SEQ ID NO:4 or a fragment thereof [encoded by at least exon 4 as set forth in Figure 2].

3. (Once Amended) The polypeptide [fragment] of claim 1, consisting of the [comprising an] amino acid sequence from residue 75 through 172 of SEQ ID NO:4 or a fragment thereof [encoded by at least exon 5 as set forth in Figure 2].

4. (Once Amended) The polypeptide [fragment] of claim 1, comprising at least the [an] amino acid sequence from residue 4 through 172 of SEQ ID NO:4 [encoded by at least exons 4 and 5 as set forth in Figure 2].

5. (Once Amended) An isolated polynucleotide encoding the polypeptide of [a fragment as in] claim 15 or a complement thereof [1].

15. (New) An isolated polypeptide selected from the group consisting of

(a) an amino acid sequence comprising SEQ ID NO:4;

(b) an amino acid sequence comprising residue 4 through 74 of SEQ ID NO:4;

(c) an amino acid sequence consisting of residue 75 through 172 of SEQ ID NO:4;

(d) a fragment of (b) or (c);

(e) an amino acid sequence comprising residue 4 through 74 of SEQ ID NO:4 and a portion of residue 75 through 172 of SEQ ID NO:4; and

(f) an amino acid sequence comprising residue 4 through 172 of SEQ ID NO:4;

wherein the polypeptide has mitogenic activity and does not consist of SEQ ID NO:2.

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16. (New) An expression vector comprising the polynucleotide of claim 5.

17. (New) A host cell comprising the polynucleotide of claim 5.

18. (New) A method of producing a polypeptide, the method comprising:

(a) culturing the polynucleotide of claim 5 under conditions suitable for formation of the polypeptide; and

(b) recovering the polypeptide.